Aerosol drug delivery: developments in device design and clinical use

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Aerosolised drugs are prescribed for use in a range of inhaler devices and systems. Delivering drugs by inhalation requires a formulation that can be successfully aerosolised and a delivery system that produces a useful aerosol of the drug; the particles or droplets need to be of sufficient size and mass to be carried to the distal lung or deposited on proximal airways to give rise to a therapeutic effect. Patients and caregivers must use and maintain these aerosol drug delivery devices correctly. In recent years, several technical innovations have led to aerosol drug delivery devices with efficient drug delivery and with novel features that take into account factors such as dose tracking, portability, materials of manufacture, breath actuation, the interface with the patient, combination therapies, and systemic delivery. These changes have improved performance in all four categories of devices: metered dose inhalers, spacers and holding chambers, dry powder inhalers, and nebulisers. Additionally, several therapies usually given by injection are now prescribed as aerosols for use in a range of drug delivery devices. In this Review, we discuss recent developments in the design and clinical use of aerosol devices over the past 10–15 years with an emphasis on the treatment of respiratory disorders.

Introduction

In recent years, increased interest in the scientific basis of aerosol therapy has given rise to a growth in technology that makes use of the inherent advantages of the inhaled route of drug administration for the treatment of both pulmonary and non-pulmonary diseases. A key advantage of this route is that it enables delivery of low doses of an aerosolised drug to its site of action for a localised effect (ie, directly to airway surfaces), which leads to a rapid clinical response with few systemic side-effects, particularly for aerosolised β-agonist therapy.[1] Drug delivery to the systemic circulation via the distal lung results in rapid absorption of the drug from this large surface area. However, when inhaled drugs are administered for effects on the airway (eg, inhaled corticosteroids), systemic absorption of the drug can give rise to unwanted side-effects.

Aerosol deposition in the lung is affected by several factors, including the aerosol-generating system, particle size distribution of the inhaled aerosol, inhalation pattern (eg, flow rate, volume, breath-holding time), oral or nasal inhalation, properties of the inhaled carrier gas (eg, carbon dioxide, heliox [a gas mixture of helium and oxygen]), airflow obstruction, and type and severity of lung disease. The distribution of target sites and local pharmacokinetics of the drug also affect clinical response. The association between drug deposition and therapeutic response led to development of aerosol drug delivery devices that have pulmonary deposition fractions of 40–50% of the nominal dose compared with the low levels of 10–15% of the nominal dose that were achieved in the past.[2] Particular inhalation patterns of specific disease states could be applied to simulate device performance under certain conditions. This simulation would enable adjustments to be made to the device to not only maximise lung aerosol deposition but also to increase the precision and consistency of aerosol drug delivery.[3] Compared with previous devices, the increased efficiency of the newer aerosol drug delivery devices means that similar efficacy can be achieved with a lower nominal drug dose.

In clinical practice, pressurised metered-dose inhalers (pMDIs) used with or without a spacer device, dry powder inhalers (DPIs), and nebulisers are used for aerosol delivery. In a 2005 systematic review, the authors concluded that these aerosol drug delivery devices were equally efficacious provided that they were used appropriately.[4] In most, but not all the trials reviewed, the investigators tested single dose strengths of β agonists in different devices. These doses were often designed to approximate the plateau of the dose-response curve, thereby limiting the ability to differentiate between devices. Only a few of these studies compared the bronchodilator responses to a

Search strategy and selection criteria

We identified references for this Review by searches of PubMed with the following search terms: "aerosol drug delivery devices", "aerosol properties/characterization", "inhalers (MDIs, spacers, dry powder inhalers)", "aerosol formulations (pressurized, powder, liquid admixtures)", "HFA and CFC propellants", "metered-dose inhalers and dose counters", "generic inhalers", "nebulizers (pneumatic, vibrating mesh, micropump)", "breath-actuated inhalers", "adaptive aerosol delivery", "aerosol therapy/inhalation therapy (bronchodilators, corticosteroids, anticholinergics)", "aerosol therapy/vaccines/gene therapy", "nanoparticles and inhalation", "inhalers and nanoformulations", "aerosol therapy and magnetic particles", "aerosol therapy and lung deposition", "aerosol therapy and pediatric respiratory disease", "aerosol therapy and asthma, chronic obstructive pulmonary disease, cystic fibrosis and other respiratory diseases", "clinical trials (aerosol delivery and clinical response, dose response)", "aerosol therapy and mechanical ventilation/artificial respiration", "aerosol therapy and non-invasive ventilation", "Heliox therapy", and "aerosol therapy and pulmonary hypertension" from January, 2000, to August, 2009. Papers published between 2004 and 2009 were given priority, but we also included papers from the early published works on aerosols that described major findings that are still pertinent today. Relevant review papers and their references were cited on the basis of their relevance. Only papers published in the English language were reviewed. Both authors are actively involved in original research in aerosol drug delivery and clinical use of therapeutic aerosols and have extensive databases for the material covered in this manuscript.

range of β-agonist doses. Since publication of that systematic review, several new devices have been marketed for clinical use and new clinical uses for inhaled therapies have emerged. Comparative trials now tend to be designed as cumulative dose-response studies or single doses over a therapeutic range.[5]

New developments in inhaler technology can take 8–10 years, and recent approaches have focused on incorporating the following features: improvement of aerosol dispersion and production of particles within the extra-fine size range needed for deep lung targeting; development of methods to reduce effort required for inhalation; and improvement of delivery efficiency while maintaining portability and ease of use of the inhaler. With generic and subsequent market entry products becoming increasingly available, in-vitro and in-vivo studies are needed to establish bioequivalence with trademarked products.[6] Some of the regulatory requirements for generics have changed in recent years, particularly for DPI generic products. For example, the appearance of the generic DPI device could be different to the originally marketed device while necessarily providing the same dose of drug to the mouth as the original and also providing aerosol characteristics that are the same.[7] Some generic DPIs have different dose strengths and different numbers of doses to the original. These products might have obtained approval as new drug products or as subsequent market entry products; the availability of the same drug in different formats can lead to confusion for clinicians prescribing and patients adhering to a treatment plan. In this Review we highlight new developments in aerosol technology and novel therapeutic uses that have emerged in recent years to help improve awareness among clinicians.

Measuring aerosol drug delivery

The inhaled route can deliver a sufficient amount of the drug to airway surfaces throughout the lung to give rise to a clinical response, although dose delivery is dependent on the adequate use of an appropriate administered drug dose and effective inhaler use. In patients with airway narrowing owing to oedema, increased secretions, or smooth muscle constriction, the distribution of inhaled aerosol is non-uniform, with increased concentrations deposited in areas of airway narrowing.[8] The amount of drug available for distribution distal to the obstructed areas is possibly reduced, which can affect clinical outcomes.[9,10] By comparing responses with the same drug from different delivery systems[11] or between different drugs within the same device category,[12] emitted dose or fine particle dose provides a more accurate estimate of the useful dose available from the inhaler than does the label claim (figures 1 and 2). Because of losses within the inhaler and on the mouthpiece,[15] drug delivery as recorded by emitted dose is less than that for the nominal dose or label claim (figure 1). Defining the unit dose depends on regulatory practices; nominal dose and label claim are interchangeable in some countries, whereas the label claim dose can be less than that for the nominal dose and equal to that for the emitted dose in other countries. For example, one of the combination therapies (fluticasone propionate/salmeterol) with a dose strength of 125 µg/25 µg in the UK is equivalent to an emitted dose of 115 µg/21 µg in the USA.

The fine particle fraction is obtained from in-vitro particle sizing of the aerosol and indicates the percentage of the aerosol mass contained in particles less than 4·7 µm. The combination of emitted dose and fine particle

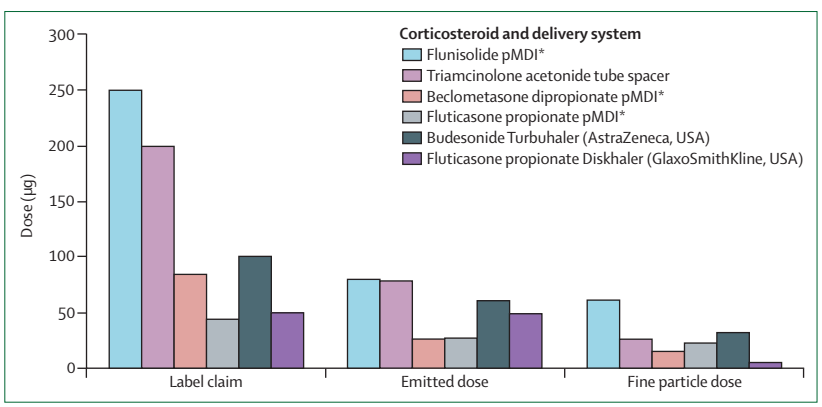

Figure 1: **Measured dose values for different inhaled pMDI and DPI corticosteroids**
Measured dose values are shown for label claim (or nominal dose), mean emitted dose, and mean fine particle dose for the inhaled pMDI and DPI corticosteroids used in the Dose of Inhaled Corticosteroids with Equisystemic Effects (DICE) trial by the National Institutes of Health and Asthma Clinical Research Network. Differences in the mass of drug available from the various inhalers used in this study led to differences in clinical response. Data plotted from Martin and colleagues;[13] figure adapted from Dolovich.[14] pMDI=pressurised metered-dose inhaler. DPI=dry powder inhaler. *pMDIs used with Optichamber (Philips Healthcare, Andover, MA, USA), a valved holding chamber.

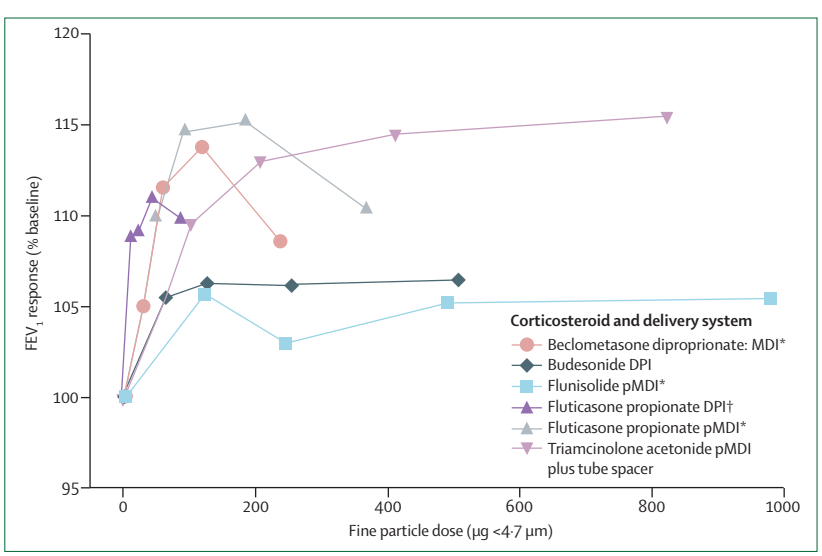

Figure 2: **FEV_1 response as a function of fine particle dose provided by six test corticosteroid inhalers**
The FEV_1 response (as a percentage of the morning measurement) is shown for the corticosteroids used in the Dose of Inhaled Corticosteroids with Equisystemic Effects (DICE) trial by the National Institutes of Health and Asthma Clinical Research Network.[13] The FEV_1 response is plotted against increasing fine particle dose—the portion of the inhaled dose likely to deposit in the lungs and give rise to a response. Reproduced from Parameswaran and colleagues,[12] with permission from Pulsus Group. FEV_1=forced expiratory volume in 1 s. MDI=metered-dose inhaler. DPI=dry powder inhaler. *pMDIs used with Optichamber (Philips Healthcare, Andover, MA, USA). †Used with Optichamber (Philips Healthcare, Andover, MA, USA), a valved holding chamber.

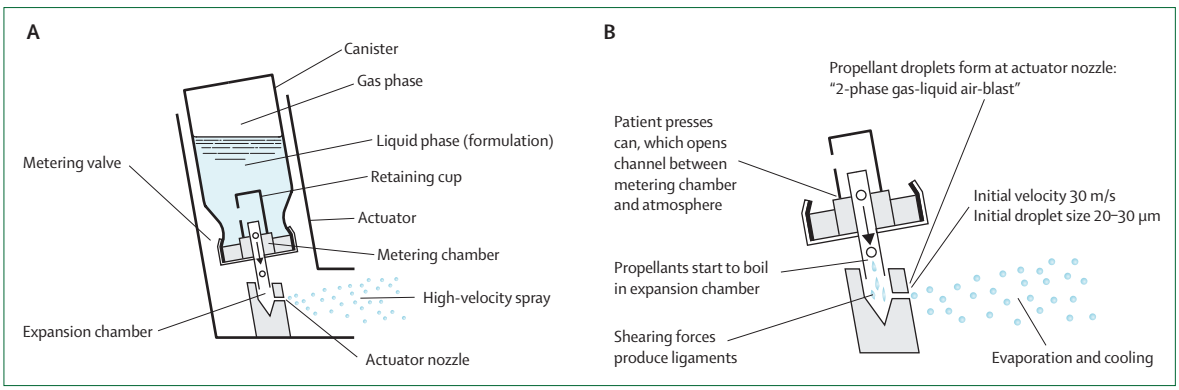

Figure 3: **Key chlorofluorocarbon MDI components and mechanisms of aerosol formation**
(A) Key components of a pMDI. (B) When the device is actuated, the drug and propellant mixture exits the metering chamber under pressure; the process by which it forms an aerosol is shown. Reproduced from Newman and colleagues,[23] with permission from the American Association for Respiratory Care.

fraction results in the fine particle mass; fine particle dose is fine particle fraction multiplied by emitted dose (figure 1), which can be associated with efficacy.[12,13,16,17] Dose metrics obtained in vitro are a useful guide for comparing device performance, assessing the likelihood of depositing drug proximally or distally in the lung, and helping to explain clinical responses. However, in addition to airway diseases, other factors such as mouth-throat geometry and inhalation flow profiles add to the variability in the deposited airway doses in vivo and therefore affect the therapeutic response.[18]

Pressurised metered-dose inhalers

pMDIs are portable, convenient, multi-dose devices that use a propellant under pressure to generate a metered dose of an aerosol through an atomisation nozzle.[19] Worldwide, pMDIs are the most widely used inhalation devices for the treatment of asthma and chronic obstructive pulmonary disease. Chlorofluorocarbon-propelled pMDIs were routinely prescribed for several decades, but in accordance with the Montreal Protocol of 1987,[20] chlorofluorocarbon propellants are being replaced by hydrofluoroalkane propellants that do not have ozone-depleting properties.[21,22] Hydrofluoroalkanes are non-toxic, non-flammable, and chemically stable and they are not carcinogenic or mutagenic. No safety concerns have been identified with their use in healthy individuals or patients with asthma. Although hydrofluoroalkane-134a and hydrofluoroalkane-227 do not affect the atmospheric ozone, they do marginally contribute to global warming.[21]

The key components of chlorofluorocarbon pMDIs (ie, canister, metering valve, actuator, and propellant) are retained in hydrofluoroalkane pMDIs (figure 3), but they have had a redesign. Two approaches were used in the reformulation of hydrofluoroalkane pMDIs. The first approach was to show equivalence with the chlorofluorocarbon device, which helped regulatory approval, and was the approach used for salbutamol pMDIs and some corticosteroid pMDIs. With the Modulite platform (Chiesi Farmaceutici, Parma, Italy), some hydrofluoroalkane formulations were matched to their chlorofluorocarbon counterparts on a microgram for microgram basis; therefore, no dosage modification was needed when switching from a chlorofluorocarbon to a hydrofluoroalkane formulation.[24] The second approach involved extensive changes, particularly for corticosteroid inhalers containing beclometasone dipropionate, and resulted in solution aerosols with extra-fine particle size distributions and high lung deposition.[25,26] The exact dose equivalence of extra-fine hydrofluoroalkane beclometasone dipropionate and chlorofluorocarbon beclometasone dipropionate has not been established, but data from most trials have indicated a 2:1 dose ratio in favour of the hydrofluoroalkane pMDI.[27] Half the dose of hydrofluoroalkane beclometasone dipropionate Autohaler (Graceway Pharmaceuticals, Bristol, TN, USA) was as effective as twice the dose of budesonide given by Turbuhaler DPI (AstraZeneca, Lund, Sweden).[28,29] However, dose equivalence of hydrofluoroalkane beclometasone dipropionate Autohaler was noted in comparison with chlorofluorocarbon fluticasone propionate.[30] Clinicians need to be aware that the Modulite platform also offers an extra-fine formulation of beclometasone dipropionate (as the Fostair inhaler with formoterol fumarate, Chiesi Farmaceutici).

The clinical implications of differences in the design and formulation of the new hydrofluoroalkane pMDIs are shown in table 1. The drug output and aerosol characteristics of salbutamol pMDIs are similar to salbutamol chlorofluorocarbon pMDIs, as are bronchodilator responses and protection against methacholine-induced[35] or exercise-induced bronchoconstriction[36] in both adults and children with asthma.[37]

Patients with asthma on regular long-term treatment with a salbutamol chlorofluorocarbon pMDI could safely transition to regular treatment with a hydrofluoroalkane pMDI without any deterioration in pulmonary function, loss of asthma control, increased frequency of hospital admissions, or other adverse effects.[22] Patients readily accept the use of hydrofluoroalkane pMDIs.[38] Salmeterol

	CFC pMDI	Changes with HFA pMDI	Clinical implication
Propellant[26]	CFCs	HFAs	HFA-134a is safe, non-toxic, and non-carcinogenic; it is rapidly metabolised and does not accumulate in tissues; it has no ozone-depleting potential and has less greenhouse effects than CFCs
Aerosol plume[26]	High velocity Cold temperature Spray emitted as a jet	Reduced velocity Warmer Rounder cloud configuration	Decreased oropharyngeal deposition Reduced chances of "cold freon" effect Difference in feel and taste
Particle size[26]	Mass median aerodynamic diameter of 3–8 µm	Suspension pMDIs similar to CFCs Solution pMDIs have lower mass median aerodynamic diameter	No major change Lower oropharyngeal deposition, enhanced deposition in the lung, especially in peripheral lung
Metering chamber[25]	Volume 50–100 µL	Smaller chamber	Less chance of leakage during storage Less chances of loss of prime (ie, the first actuation after storage contains a reduced drug dose)
Formulation[22]	Creaming of suspension Variable puff-to-puff dosing Tail-off effect* No ethanol content[31]	Suspension or solution with ethanol Improved puff to puff dosing Only a few additional doses provided after specified number of doses on label claim Ethanol used as solvent or co-solvent	No need to shake the aerosol before use for solution pMDIs More consistent clinical efficacy Less chance of misuse because spray content decreases substantially when additional actuations are used beyond the specified number of doses on the label claim Blood ethanol concentrations might lead to failed breath-analyser test within 3 min of inhaling two doses
Priming[22]	Needs priming before initial use if not used for 4 days	Variable priming requirements	Check priming instructions according to brand
Actuator orifice	Orifice diameter 0·14–0·6 mm	Smaller sized aperture Finer aerosol particle size	Greater chances of clogging with potential to change aerosol characteristics; recommended to wash actuator once weekly or if spray force decreases Reduced oropharyngeal deposition; in combination with reduced spray velocity enhances efficiency of drug deposition in the lung
Dose counter[32,33]	No dose counter	Dose counter on some devices	Less chance of underdosing or overdosing as patients can count the number of doses used and establish when canister is nearly empty
Moisture affinity	Moisture leaks into canister	Increased moisture affinity	Some HFA pMDIs (eg, Ventolin, GlaxoSmithKline, Ware, UK) have lower shelf-life after being removed from water-resistant packaging pouch
Temperature dependence	Operates best in warm temperature	Less temperature dependence	Less chance of losing efficacy in cold weather Substantial reduction in dose below 10°C
Cost[34]	Generic inhalers inexpensive	Higher cost of trademarked pMDIs	Could change cost-benefit of using pMDIs Patients might forego treatment or choose cheaper and less effective alternatives

CFC=chlorofluorocarbon. pMDI=pressurised metered-dose inhalers. HFA=hydrofluoroalkane. *Variability in quantity of drug in actuations past the number of doses in the canister as specified by the label claim, resulting in less uniform drug doses.

Table 1: **pMDIs: problems with CFC-propelled pMDIs, changes made with HFA-propelled pMDIs, and clinical implications of modification**

hydrofluoroalkane pMDIs (Serevent, GlaxoSmithKline, Ware, UK) and hydrofluoroalkane combinations of long-acting β agonists and corticosteroids (Advair, GlaxoSmithKline, Ware, UK; Symbicort, AstraZeneca, Lund, Sweden) have similar efficacies as the chlorofluorocarbon formulations.[39] Coordinated efforts by device manufacturers, pharmaceutical companies, regulatory agencies, and health-care providers have resulted in minimum disruption in the transition from chlorofluorocarbon to hydrofluoroalkane pMDIs.

Breath-actuated MDIs

Problems in precisely coordinating device actuation with inhalation lead to poor drug delivery, sub-optimum asthma control, and increased inhaler use. Breath-actuated pMDIs, such as the Maxair Autohaler (Graceway Pharmaceuticals, Bristol, TN, USA) and Easibreathe (IVAX, Miami, FL, USA), were developed to overcome the problem of poor coordination between pMDI actuation and inhalation. The devices consistently actuate early in inspiration at an inspiratory flow rate of about 30 L/min and are uniformly well accepted by patients,[40] with fewer than 5% of patients unable to achieve the threshold inspiratory flow rate required for actuation.

Patients who used the Maxair Autohaler achieved higher pulmonary deposition (21%) than did patients who had poor coordination while using a conventional chlorofluorocarbon pMDI (7%), but the clinical effects for both groups were similar.[41] Some investigators reported improved outcomes with breath-actuated pMDIs,[29] but changes in formulations, particle size, and fine particle dose could account for the differences reported. Increased use of breath-actuated inhalers might improve asthma control[42] and reduce overall cost of asthma therapy compared with conventional pMDIs. However, oropharyngeal deposition with breath-actuated pMDIs is as high as that with chlorofluorocarbon pMDIs. As breath-actuated devices cannot be used with valved holding chambers, the oropharyngeal side-effects from corticosteroids could be a problem for some patients. Moreover, gastrointestinal absorption of some

inhaled corticosteroids, such as beclometasone dipropionate, could lead to an increased frequency of systemic side-effects.

Other pMDI technologies that provide more precise targeting of the respiratory tract include the Vortex Nozzle Actuator (Kos Pharmaceuticals, Morrisville, NC, USA), Synchro-Breathe (Vortran Medical Technology, Sacramento, CA, USA), and Tempo Inhaler (MAP Pharmaceuticals, Mountain View, CA, USA).

Dose counters

Dose counters provide a reliable method for patients to monitor their use of drugs. As the overfill is typically 10%, pMDIs can continue to function after the labelled number of doses has been given, but the amount of drug in each spray can be inconsistent, especially for chlorofluorocarbon products. Mechanical dose counters are accurate and reliable,[32] whereas add-on dose counters, such as the Doser device (MediTrack Products, Hudson, MA, USA) might lose accuracy over time.[43] The MD Turbo (Teamm Pharmaceuticals, Morrisville, NC, USA), or other electronic devices, are not widely used in clinical practice.[43]

Spacers and holding chambers

Spacer devices are categorised as add-on devices, extension devices, or holding chambers and they improve efficacy by providing more reliable delivery of pMDI drugs to patients who have difficulty in coordinating inhalation with pMDI actuation.

Spacer devices have three basic designs—the open tube, the reservoir or holding chamber, and the reverse-flow design, in which the pMDI, placed close to the mouth, is fired in the direction away from the patient. Adding a one-way valve creates a holding chamber, enabling retention of aerosol within the chamber for a finite time after pMDI actuation. Holding chambers produce a fine aerosol because of the high level of impaction of larger drug particles and partial evaporation of propellant within the chamber.[44] As substantial differences exist between these three categories of spacer design, the most appropriate spacer for the patient's age and ability to self-treat should be carefully considered.

Device-related factors contribute to variability in drug delivery.[45] For example, larger-volume spacers and holding chambers capture and retain more of the aerosol cloud, whereas smaller-volume spacers and holding chambers reduce the amount of available aerosol generated from the impaction of the formulation on their walls. The characteristics of various spacers and effects on delivery, lung deposition, and clinical efficacy of inhaled drugs are well described elsewhere.[21]

Electrostatic charge

Drug deposits can build up on walls of plastic spacers and holding chambers, mostly because of electrostatic charge. Aerosols remain suspended for longer periods within holding chambers that are manufactured from non-electrostatic materials than other materials (figure 4A). Thus, an inhalation might be delayed for 2–5 s without a substantial loss of drug to the walls of metal or non-conducting spacers.[46,47] The electrostatic charge in plastic spacers can be substantially reduced by washing the spacer in mild detergent followed by a water rinse to prevent inhalation of dried detergent particles.

In children with asthma, salbutamol delivered through plastic spacers has a similar efficacy to that delivered through non-electrostatic or metal spacers.[48] In patients with chronic obstructive pulmonary disease, tiotropium delivered from a pMDI through a non-static spacer provided a similar clinical benefit to that given by the trademarked DPI.[49] An increased fine particle dose available from antistatic spacers could lead to an increased number of systemic adverse effects with long-term inhaled corticosteroids use. For example, more adrenal suppression was reported after the hydrofluoroalkane fluticasone propionate was delivered through two antistatic plastic spacers and one metal spacer than that reported with the pMDI alone.[50]

Facemask interface

A valved holding chamber fitted with an appropriate facemask is used to give pMDI drugs to neonates, young children, and elderly patients.[51] The two key factors for optimum aerosol delivery are a tight but comfortable facemask fit and reduced facemask dead space.[52–54] Because children have low tidal volumes and inspiratory flow rates, comfortable breathing through a facemask requires low resistance inspiratory or expiratory valves.

Inhalation technique

All young children should be given a holding chamber-type spacer with their pMDI, otherwise inhalation of pMDI aerosols is likely to be inefficient in more than 50% of patients.[55] Tidal breathing from a holding chamber and facemask should be encouraged in patients who are unable to use pMDIs appropriately. In preschool children who were less than 5 or 6 years of age, two to six tidal breaths seem to be sufficient to inhale the aerosol. In infants and young children, the tidal volume (based on the child's weight if not possible to measure directly) to spacer volume ratio should be taken into account when selecting a spacer device.[56]

Dry powder inhalers

Several new, innovative DPIs are available for the treatment of asthma and chronic obstructive pulmonary disease[57] (figure 4B) and for delivery of a range of other drugs such as proteins, peptides, and vaccines.[58] The challenge is to combine suitable powder formulations with DPI designs that generate small particle aerosols.[59,60]

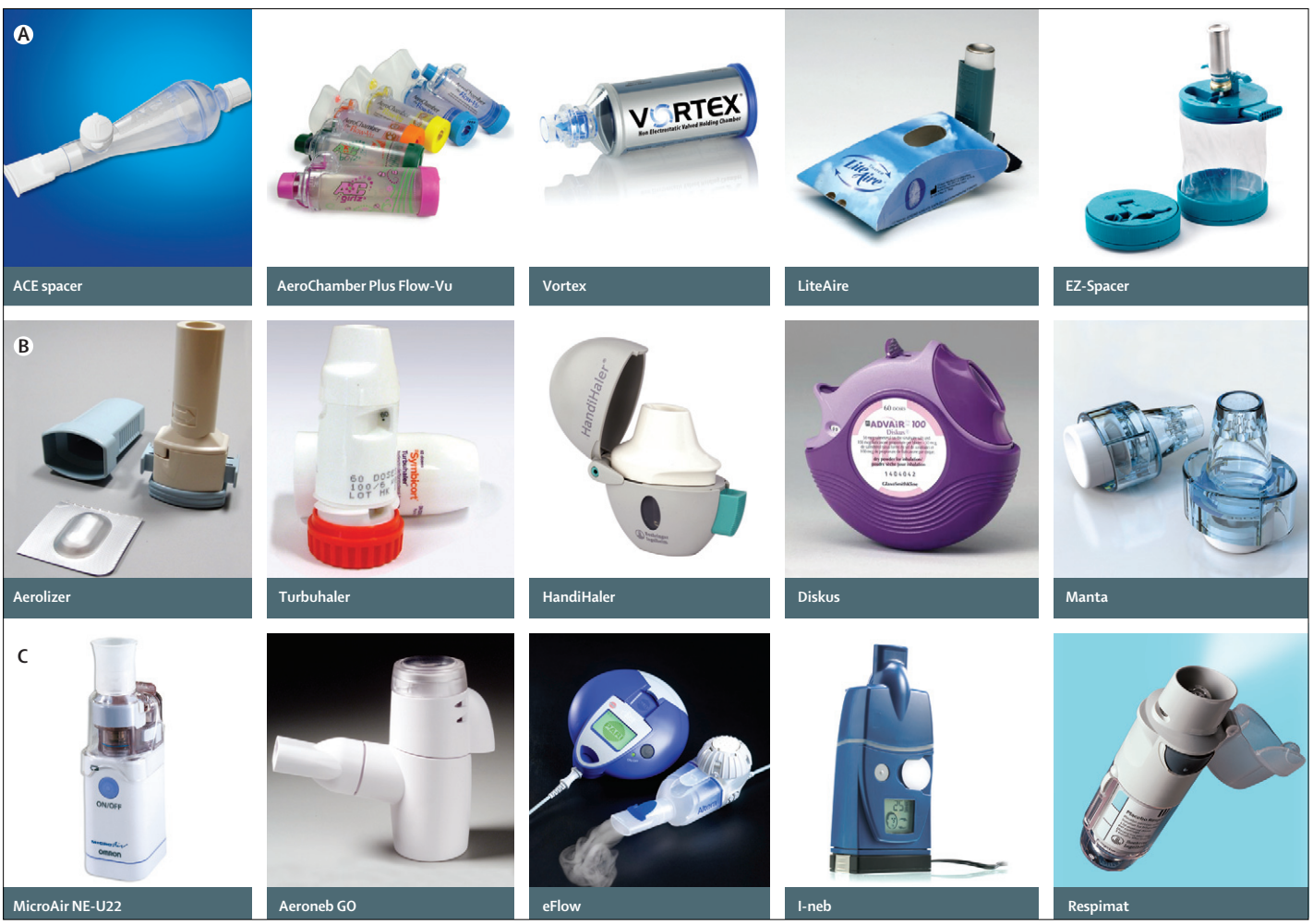

Figure 4: **Examples of marketed spacers and holding chambers, dry-powder inhalers available by prescription or in development, and nebulisers that incorporate new-generation technology**
(A) The ACE spacer (Smiths Medical, Rockland, MA, USA), the EZ-Spacer (FSC Laboratories, Charlotte, NC, USA), and the Inspirease spacer (not shown) are examples of reverse-flow designs; AeroChamber Plus Flow-Vu (Trudell Medical International, London, ON, Canada), Vortex (PARI Respiratory Equipment, Midlothian, VA, USA), and Nebuchamber (AstraZeneca, Lund, Sweden; not shown) are examples of metal or non-conducting valved holding chambers. The LiteAire (Thayer Medical, Tucson, AZ, USA) is a collapsible, disposable, valved paper spacer. (B) The Aerolizer (Schering Plough, Kenilworth, NJ, USA) and Handihaler (Boehringer-Ingelhein, Ingelheim, Germany) dry-powder inhalers are capsule devices; the Turbuhaler (AstraZeneca, Lund, Sweden) is a reservoir dry-powder inhaler; the Diskus (GlaxoSmithKline, Ware, UK) is a multi-unit dose dry-powder inhaler with single doses of drug encapsulated in foil blisters; the Manta single-dose dry-powder inhaler (Manta Devices, Boston, MA, USA) is a disposable, low-cost inhaler that uses a foil blister for drug storage with a unique internal opening technology. (C) The MicroAir NE-U22 (Omron, Vernon Hills, IL, USA), Aeroneb GO (Aerogen, Galway, Ireland), eFlow (PARI, Midlothian, VA, USA), and I-neb (Respironics, Murrysville, PA, USA) incorporate vibrating mesh or vibrating plate aerosol generators. I-neb and Prodose (Profile Therapeutics, Bognor Regis, UK; not shown) use adaptive aerosol delivery technology for drug delivery. The Respimat inhaler (Boehringer-Ingelheim, Ingelheim, Germany) is the first of a new class of hand-held inhalers called soft mist inhalers. Both the Respimat and the AERx (Aradigm, Hayward, CA, USA; not shown) are high efficiency devices that use precise dosimetric systems. The Respimat inhaler has a multi-dose capability.

Use of DPIs is expected to increase with the phasing out of chlorofluorocarbon production along with increased availability of drug powders and development of novel powder devices.[22,57]

Powder storage

DPI doses can be pre-metered in the form of single capsules or foil blisters or as multi-single unit dose disks; alternatively, device metering of bulk powder can be done with reservoir devices. As drug delivered from a DPI mainly depends on the ability of the patient to generate a sufficient pressure drop across the device on inhalation, inconsistent efforts by the patient could result in substantial variability between doses. With a capsule-based DPI, the patient can take a second inhalation if powder clearly remains in the capsule after the initial breath.

Form and function

Breath actuation is a major advantage of DPIs over pMDIs. However, exhalation into a DPI could result in the loss of the dose positioned in the inhalation channel. For reservoir DPIs, the powder remaining in the reservoir can, over time, be affected by added humidity in the exhaled breath. DPIs that rely on the inspiratory effort of the patient to dispense a dose (passive or

patient-driven devices) ensure delivery on inhalation, but a sufficient inspiratory flow rate is needed to aerosolise the drug powder. Other DPI designs (active or power-assisted designs) incorporate battery-driven impellers and vibrating piezoelectric crystals that reduce the need for the patient to generate a high inspiratory flow rate, an advantage for many patients. In power-assisted DPI designs, the powder is released from storage by external means, such as directing compressed air through the DPI, and is then held in a storage or valved holding chamber. Enhanced sedimentation of drug particles in the chamber reduces the dose of drug released and decreases the particle size of the powder dispensed.

Resistance and performance

Drug delivery to the lung ranges between 10% and 37% of the emitted dose for several marketed DPIs.[61] Recent improvements in DPI design enable the dose to be dispensed independent of inspiratory flow rate between 30 L/min and 90 L/min. DPIs with medium resistance to airflow are designed to operate at an optimum rate of 60 L/min, but even this flow rate might be difficult to achieve for some patients, especially elderly patients with severe chronic obstructive pulmonary disease.[62] Although flow independence is advantageous for consistent drug delivery from a DPI, this independence could be a disadvantage when adult doses are given to children. The risk of overmedicating children with these DPIs could be partly offset by the low inspiratory volumes of children. Dose titration should be done to avoid overdosing.

The physical design of the inhaler establishes its specific resistance to airflow (measured as the square root of the pressure drop across the device divided by the flow rate through the device), with current designs having specific resistance values ranging from about 0·02–0·2 ($cmH_2O^{1/2}$/(L/min). With high-resistance devices, breathing at the optimum inspiratory flow rate for the particular DPI selected helps to produce a fine powder aerosol with increased delivery to the lung. Children younger than 6 years cannot consistently inhale from a DPI with the proper inspiratory flow rate and pMDIs with valved holding chambers are preferable.[63] Children older than 6 years can successfully use a DPI even during acute asthma exacerbations.[64]

Other factors for device use

Because of variations in the design and performance of DPIs, patients might not use all DPIs equally well. Therefore, DPIs that dispense the same drug might not be readily interchangeable.[65] Dose counters in new-generation DPIs provide patients with either a numerical display of the number of doses remaining or a colour indicator as a reminder to renew their prescription in time.

Nebulisers

Nebulisers are devices that convert a liquid in solution or suspension into small droplets.

Pneumatic or jet nebulisers

Jet nebulisers use compressed gas flow to break up the liquid into a fine mist—the protruding surfaces of primary and/or secondary baffles within the nebuliser are positioned in the path of the aerosol created so that the large liquid droplets impinge upon them, leading to a reduced and more useful particle size of the exiting aerosol.[66] Substantial variances in nebuliser performance are caused by differences in their design, the source of energy (compressed gas or electrical compressor), gas flow and pressure, connecting tubing, interface used (spacer, and mouthpiece or mask), and the breathing pattern of the patient.

Unlike pMDIs and DPIs, no special inhalation techniques are needed for optimum delivery with nebulisers. However, conventional nebulisers, which need compressed gas or a compressor to operate, are generally not portable; they have poor delivery efficiency and treatment times are much longer than that for pMDIs and DPIs.

Substantial aerosol wastage with continuously operated jet nebulisers could be reduced by attaching a T-piece and corrugated tubing or a reservoir bag to collect aerosol generated during exhalation (Circulaire, Westmed, Tucson, AZ, USA)—drug aerosol is then inhaled from the reservoir with the next inspiratory breath.[67] Breath-enhanced and dosimetric nebulisers reduce drug loss during exhalation by incorporating design features such as one-way valves.[68] These features have been used for delivery of pentamidine, with filters placed in the expiratory tubing to prevent environmental contamination with pentamidine after exhalation.

Ultrasonic nebulisers

In these devices, sound waves generated by vibrating a piezoelectric crystal at high frequency (>1 MHz) are transmitted to the surface of the drug solution, resulting in the formation of standing waves. The crests of these waves are then broken up into droplets. The precise mechanism of aerosol generation by ultrasonic nebulisers is not yet fully understood.[69] Older models of ultrasonic nebulisers are costly and bulky and have a tendency to malfunction. Moreover, compared with newer ultrasonic designs, their relative inefficiency in nebulising drug suspensions, liposomes, or more viscous solutions are major limitations to their use.

Effect of formulation

The presence of a preservative in a drug solution and admixture with other drugs affect nebuliser output and aerosol characteristics.[70,71] Drug mixtures need to be physically and chemically compatible.[72,73] Since July, 2007, the US Centers for Medicare and Medicaid Services

stopped reimbursement for pharmacy-compounded nebuliser drugs.

Delivery by mouthpiece versus facemask

Aerosol deposition in the nasal passages substantially reduces pulmonary drug delivery and bronchodilator efficacy;[74] however, facemasks might be necessary for the treatment of acutely dyspnoeic or uncooperative patients. For optimum efficacy, the facemask should produce a tight seal[75,76] to avoid aerosol leakage and aerosol deposition around the eyes. The orientation of the nebuliser with regard to the facemask affects the pattern of aerosol deposition. Although "front-loaded" masks (ie, in which the nebuliser is inserted directly into the facemask in front of the mouth) provide more aerosolised drug, they also produce greater facial and ocular deposition than do "bottom-loaded" masks (ie, in which the aerosol enters the mask from below the mouth).[77] Aerosol deposition on the face and eyes could be reduced by use of a prototype mask that incorporates vents in the mask and has cut-outs in the eye region.[3,77]

Continuous aerosol delivery

In patients with acute severe asthma, short-acting bronchodilators (eg, salbutamol 5–15 mg/h) are commonly given continuously[78] with large-volume nebulisers or the high-output extended aerosol respiratory therapy nebuliser, which can provide consistent drug output for 4 h[70] to 8 h,[79] respectively. Patients with acute asthma have some benefits from continuous bronchodilator therapy in the emergency department.[80]

Nebuliser and compressor combinations

Nebuliser performance for use at home depends on the choice of an appropriate compressor,[81] and some nebuliser manufacturers specify the compatible compressors for optimum performance (eg, PARI LC Plus Reusable Nebuliser and DeVilbiss Pulmo-Aide compressor [Somerset, PA, USA] for inhalation of tobramycin).

Multi-dose liquid inhalers

The Respimat inhaler (Boehringer-Ingelheim, Ingelheim, Germany)[82] is a novel aerosol drug delivery device that uses the energy from a compressed spring to force a metered dose of the liquid drug formulation through a narrow nozzle system created using microchip technology. The aerosol produced has a high fine particle fraction and a high efficiency of pulmonary drug delivery, up to 50% for some formulations.[83] This inhaler is available for clinical use in Europe but has not yet been approved in North America.

Vibrating mesh or aperture plate nebulisers

Figure 4C shows the characteristics of nebulisers that use a vibrating mesh or plate with several apertures[84–86]—Aeroneb (Aerogen, Galway, Ireland), MicroAir (Omron, Vernon Hills, IL, USA), eFlow (PARI, Midlothian, VA, USA), and I-neb (Respironics, Murrysville, PA, USA)—and these are compared with conventional jet and ultrasonic nebulisers in table 2. The aerosol characteristics depend on the physicochemical properties of the solution.[87,88] Vibrating mesh or vibrating plate nebulisers have a higher lung deposition,[85] negligible residual volumes, a faster rate of nebulisation than do jet nebulisers, and they effectively nebulise solutions and suspensions, as well as liposomal formulations,[89] proteins, such as α-1 antiprotease[90] and dornase alfa.[91] Denaturation of non-complexed, supercoiled DNA occurs during nebulisation, which is similar to jet nebulisers.[69] In patients with cystic fibrosis, vibrating mesh nebulisers efficiently deliver tobramycin,[92] and escalating doses of aztreonam lysinate.[93] The residual volume varies with the design of the eFlow device by PARI. One design of the eFlow device has a low residual volume to minimise drug wastage, whereas another design has a larger residual volume, which is comparable to that in jet nebulisers. Although the efficiency of drug delivery in the latter design is comparable to breath-enhanced jet nebulisers, treatment times are shorter with the eFlow.

The cost of these vibrating mesh and vibrating plate devices is comparable to that of ultrasonic nebulisers, but is much higher than that of conventional jet nebulisers. All vibrating mesh and vibrating plate nebulisers must be cleaned regularly to prevent build-up of deposit and blockage of the apertures, especially when suspensions are aerosolised.

	Jet	Ultrasonic	Vibrating mesh
Features			
Power source	Compressed gas or electrical mains	Electrical mains	Batteries or electrical mains
Portability	Restricted	Restricted	Portable
Treatment time	Long	Intermediate	Short
Output rate	Low	Higher	Highest
Residual volume	0·8–2·0 mL	Variable but low	≤0·2 mL
Environmental contamination			
Continuous use	High	High	High
Breath-activated	Low	Low	Low
Performance variability	High	Intermediate	Low
Formulation characteristics			
Temperature	Decreases*	Increases†	Minimum change
Concentration	Increases	Variable	Minimum change
Suspensions	Low efficiency	Poor efficiency	Variable efficiency
Denaturation	Possible‡	Probable‡	Possible‡
Cleaning	Required, after single use	Required, after multiple use	Required, after single use
Cost	Very low	High	High

*For jet nebulisers, the temperature of the reservoir fluid decreases about 15°C during nebulisation because of evaporation. †For ultrasonic neubulisers, vibration of the reservoir fluid causes a temperature increase during aerosol generation, which can be as high as 10–15°C. ‡Denaturation of DNA occurs with all the nebulisers.

Table 2: **Comparison of different nebulisers**

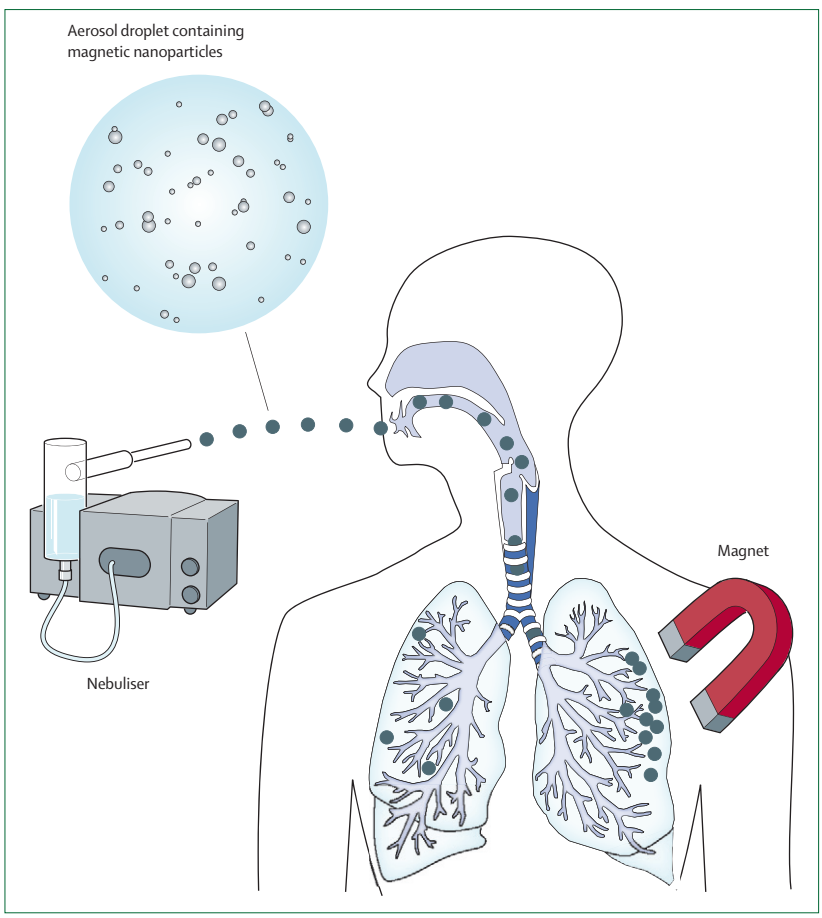

Figure 5: **Mechanism of action of nanomagnetosols**
Magnetic nanoparticles are mixed with the drug solution but the drug is not actually bound to the particles, thus magnetic nanoparticles do not have to be formulated specifically for each drug. Because each aerosol droplet contains many magnetic particles, they appear as a large magnetic particle to an external magnetic field. The increased size of the aerosol droplets improves the ability to guide the nanoparticles to the desired region(s) of the lung by use of a strong external magnetic field. Reproduced from Plank,[102] with permission from Elsevier.

Adaptive aerosol delivery

These devices use software-driven monitoring and control systems that monitor inspiratory flow, breathing frequency, and inspiratory time, providing aerosol delivery only during inspiration. The I-neb and Prodose system (Profile Therapeutics, Bognor Regis, UK) use an adaptive aerosol delivery disc—a plastic disc containing a microchip and antenna—to control drug delivery.[94] The I-neb is a vibrating mesh nebuliser, whereas the Prodose is powered by a compressor. In addition to delivering a precise drug dose, other useful features of the I-neb are the provision of feedback to the patient on dose completion along with details of each treatment. These data can be transmitted via a modem to a remote location, which enables continuing assessment of adherence of the patient to the drug regimen. The Pulmonary Drug Delivery System Clinical (Nektar Therapeutics, San Carlos, CA, USA), another breath-synchronised, high-efficiency vibrating plate nebuliser, can be used both during mechanical ventilation and spontaneous breathing. Other novel nebuliser systems include the AKITA system (Activaero, Gemuenden, Germany),[95] the Small Particle Aerosol Generator (ICN Pharmaceuticals, Costa Mesa, CA, USA),[96] and humidified high-flow nasal cannulae.[97]

Targeting aerosol delivery in the lung

The ability to target drugs to specific sites of disease is a major unmet need of aerosol therapy.

Passive targeting

The "passive targeting" approach directs deposition mainly to the airways or preferentially to the more peripheral airways and alveolar compartment by modification of aerosol droplet size,[2] breathing pattern, depth and duration of holding a breath, timing of the aerosol bolus in relation to inspiratory airflow, drug-aerosol dosage, and density of the inhaled gas.[2,4] Similarly, a substantial fraction of the inhaled aerosol can be deposited at areas of airway narrowing during exhalation, especially when flow-limited segments are present.[3] Airway targeting can also reduce oropharyngeal drug deposition, thereby reducing the risk of local[98] and systemic[99] side-effects resulting from the swallowed dose.

Active targeting

The "active targeting" approach localises drug deposition by directing the aerosol to the diseased area of lung or, alternatively, by using molecular or biological recognition, providing a more controlled and reproducible delivery to predetermined targets in the lung than by passive targeting. For example, the AeroProbe intracorporeal nebulising catheter (TMI, London, ON, Canada) could be inserted into the working channel of a fibre-optic bronchoscope to deliver genes[100] or chemotherapeutic drugs[101] directly to a lung lobe.

Recently, inert superparamagnetic iron oxide nanoparticles added to the nebuliser solution were used to guide aerosol to the affected region of the lung by means of a strong external magnetic field (figure 5).[103] A range of therapeutic agents, including genes, could be packaged for delivery by this technique.[102]

Heliox

Heliox (a gas mixture of 80% helium and 20% oxygen), which has one-third the density of air, results in more peripheral deposition of inhaled aerosol particles than does air, especially in the presence of airway constriction. In children with airway obstruction, the rate of aerosol deposition is enhanced while breathing heliox compared with breathing oxygen.[104]

When heliox, rather than air or comparable mixtures of oxygen and air, is the driving gas in a ventilator circuit, aerosolised drug delivered from a pMDI is increased.[105] By contrast, drug output from a nebuliser decreases when it is operated with heliox instead of air.[106] To ensure adequate nebuliser output with heliox, the flow of heliox

has to be increased from the conventional 6–8 L/min to 15 L/min.[105] Similar changes occur when vibrating mesh nebulisers use heliox rather than air.[107]

Aerosol delivery during mechanical ventilation

Drug delivery to patients on mechanical ventilation is complicated by the presence of an artificial airway. The major factors that affect the efficiency of drug delivery during mechanical ventilation include: the position of the patient, the aerosol generator and its configuration in the ventilator circuit, aerosol particle size, synchronisation of aerosol generation with inspiratory airflow from the ventilator, conditions in the ventilator circuit, and ventilatory measurements. Dhand and Guntur[108] provide further discussion on the methods to optimise aerosol therapy in this setting and the use of inhaled therapies in adult, paediatric, and neonatal patients. Nebulisers and pMDIs, but not DPIs, are routinely used for bronchodilator therapy in mechanically ventilated patients. With optimum techniques of administration, the efficiency of aerosol drug delivery achieved with these devices is comparable to that in ambulatory, non-intubated patients. Similarly, as with ambulatory patients with chronic obstructive pulmonary disease, combination therapy with short-acting β agonists and anticholinergic drugs produces additive bronchodilation in ventilator-supported patients.

Aerosol delivery in patients receiving noninvasive positive pressure ventilation is less efficient than that in patients receiving invasive mechanical ventilation.[109]

Non-conventional therapeutic uses

Vaccines

Flumist (MedImmune, Gaithersburg, MD, USA), a live attenuated influenza vaccine given by nasal spray,[110] and other inhaled spray-dried formulations containing whole inactivated virus or split subunit vaccine, could be used for influenza prevention.[111] In the early 1990s, about 4 million children were immunised against measles with the Classical Mexican Device—a home-built system that incorporated a jet nebuliser from IPI Medical Products (Chicago, IL, USA). Aerosolised vaccine against measles provided a stronger and more durable boosting response than did vaccination by injection in school-age children[112] and is now being tested by WHO in mass immunisation campaigns.[113] Similarly, an inhaled measles and rubella vaccine,[114] a triple vaccine (measles, mumps, and rubella),[115] a dry powder formulation of live attenuated measles vaccine,[116] and inhaled vaccines for protection against inhaled bioterrorism agents such as anthrax and tularaemia are under development.[117,118]

Inhaled prostanoids

Epoprostenol (an intravenous prostacyclin) improves survival in patients with pulmonary arterial hypertension, but, compared with intravenous administration, aerosolised prostacyclins have a higher selectivity for intrapulmonary effects with few systemic effects.[119] Iloprost, a stable analogue of prostacyclin, has a longer half-life than prostacyclin (20–30 min vs ~3 min), producing pulmonary vasodilation for 30–90 min. Six to nine inhalations of iloprost daily improved exercise capacity, functional capacity, and pulmonary haemodynamics in patients with pulmonary arterial hypertension with few side-effects.[120] The combination of inhaled iloprost with oral sildenafil[121] or oral bosentan[122] further enhanced and prolonged the pulmonary vasodilator effects. Inhaled treprostinil, another prostacyclin analogue, had a more prolonged pulmonary vasodilator effect than did inhaled iloprost.[123]

Inhaled ciclosporin

Aerosolised ciclosporin prevents or delays post-lung transplant rejection and improves survival compared with an immunosuppressive regimen without aerosolised ciclosporin.[124]

Gene therapy

Aerosolised gene therapy could be used to correct specific genetic abnormalities in patients with cystic fibrosis and α-1 antitrypsin deficiency[125] and possibly for the treatment of lung cancer[126] and other non-genetic diseases, such as pulmonary hypertension and acute lung injury.

Nebulisation of liquid-suspended gene particles, although inefficient, remains the mainstay for inhaled gene therapy. Because of its viscosity, the concentration of DNA that can be readily nebulised is less than 5 mg/mL. Fragmentation owing to shear stresses, preferential nebulisation of solute, and adhesion of DNA to plastic surfaces results in less than 10% of the DNA in the nebuliser cup being emitted from the nebuliser.[69,127]

Device selection

The appropriateness of a device for a patient in a given clinical situation depends on several factors. The following questions should be asked before making a selection. In what devices is the drug being prescribed available and how do these different devices compare in terms of ease of use, performance, clinical efficacy, and safety? Is the device likely to be available for several years? Do the published works support the advertised in-vitro performance information of reliable and reproducible aerosolised drug delivery and its clinical efficacy with a minimum or no side-effect profile? Is the device patient-friendly with regard to operation and maintenance? Is the device clinically useful on a broad scale (ie, can it be used to treat different patient populations in various clinical settings and patients in different age-groups)? Is the device cost effective in terms of purchase price, price to maintain, and cost to train caregivers in use and to teach patients? Is the device reusable and can it be used with many drugs? And is reimbursement available for the device?

Correct use of aerosol drug delivery devices is important for successful therapy. Patients, physicians,

and other healthcare workers must be adequately instructed in the proper use of aerosol devices prescribed.[128] Additionally, adherence to the therapeutic regimen must be emphasised to the patient or caregiver.[129] Reviewing the patient's inhaler technique on subsequent office or clinic visits is important for good disease management and to maintain adherence of the patient to therapy.[16] If the selected delivery device does not provide satisfactory treatment or results in unacceptable side-effects, other equally effective options are available.[4]

Conclusions

In the past 10–15 years, several innovative developments have advanced the field of inhaler design. There are many choices in all device categories that incorporate features providing efficient aerosol delivery to treat various lung and systemic diseases. Attempts to improve topical delivery to selective areas of the lung or new approaches to access the distal lung for systemic therapy are continually being investigated and they have the potential to provide more advanced aerosol drug delivery technologies than those currently available.

Contributors

Both authors contributed equally to the preparation of this paper.

Conflicts of interest

Within the past 5 years, MBD has received research grants from Pfizer, GlaxoSmithKline, and AstraZeneca, and has received consultancy fees from Cogentus Pharmaceuticals, Novartis Imaging, AstraZeneca, and Boehringer Ingelheim. MBD has consulted for Medicines in Need but did not receive any fees. Within the past 5 years, RD has received speaker fees from GlaxoSmithKline, Boehringer-Ingelheim, Pfizer, and Bayer, consultancy fees from Novartis and Bayer, and research support from Sepracor and Trudell Medical International. RD was a principal site investigator for a clinical trial sponsored by Novartis.

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